REMARKS

I. Examiner Interviews:

Applicants thank Examiners Stephen Rawlings and Brad Duffy for the courtesy of two telephonic Examiner's interviews with the undersigned and her associate, Dr. Joseph Koipally, conducted on October 22, 2009 and November 18, 2009, respectively. At the Interview conducted on October 22, 2009, the novelty rejection over Fukishima *et al.* (U.S. Pat. Publ. No. 2004/058393), the indefiniteness rejections, and possible claim amendments were discussed. Based on the discussions at this interview, Applicants prepared and forwarded to the Examiners proposed claim amendments prior to the second interview. At the Interview conducted on November 18, 2009, the Examiners made some additional suggestions for improving the claims. These suggestions have been incorporated in the present amendment. The Examiners indicated that the amendments would likely result in the removal of the outstanding rejections, though said that a new search would likely be necessary before the claims could be allowed. During the November 18, 2009 Interview, Applicants noted that claims drawn to specific anti-mpl minibodies were being pursued in a separate case, U.S. Appl. No. 10/551,504.

II. Status of Claims:

Upon entry of the instant amendment, claims 40-42, 49, 50, 54, and 59 will be under examination in this application, claims 1-19 having been previously canceled, claims 20-39 not entered, claims 43-48 , 51-53, 56, and 57 canceled herein without prejudice, and claims 55-58 withdrawn as being drawn to a non-elected invention. Claims 40, 41, 54, 55, and 59 are amended. Support for the claim amendments can be found throughout the application as filed, *e.g.*, at page 4, lines 2-30; page 6, lines 30-33; page 7, lines 17-24; page 14, lines 2-4 and 28-35; and Example 2.7 at pages 26-27. No new matter is added.

III. Comment on Withdrawn Claims:

The Action indicates that claims 55-58 have been withdrawn as drawn to a non-elected invention. However, the Action does not address Applicants' arguments for rejoinder of

claims 55-58 in the Response filed April 8, 2009. For the Examiner's convenience, Applicants reproduce those arguments below:

> Applicants note that the prior Examiner assigned to this application, Examiner Gussow, reviewed with her supervisor a set of claims essentially identical to claims 40-59 and informed Applicants by telephone on June 25, 2008, that the claims were indeed within the same restriction group as original claims 1-8 and 13, and therefore could be presented in this application. That interview with Examiner Gussow and her supervisor is described on pages 7-8 of the Reply filed by applicants on June 30, 2008.
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> Given the prior determination by the Office that claims essentially identical to 55-58 fall within the elected restriction group, Applicants respectfully request that the Examiner reconsider the withdrawal of claims 55-58 and rejoin these claims with the claims under examination. If it would be helpful to add a preamble such as "A method for enhancing antibody activity" to the withdrawn claims, Applicants would consider doing so. (*see,* page 7, Election/Restriction, second and third paragraphs).

Applicants would also note, in this context, that MPEP § 704.01 states:

> When an examiner is assigned to act on an application which has received one or more actions by some other examiner, full faith and credit should be given to the search and action of the previous examiner unless there is a clear error in the previous action or knowledge of other prior art. In general the second examiner should not take an entirely new approach to the application or attempt to reorient the point of view of the previous examiner, or make a new search in the mere hope of finding something.

During the October 22, 2009, Interview, the Examiners indicated that, since Examiner Anne Gussow had previously decided that claims 55-58 are within the present restriction group, that decision would be considered in deciding whether to permit rejoinder. Claims 56 and 57 are presently canceled, so the issue is moot as to them. In view of the foregoing, Applicants respectfully request that the Examiner rejoin claims 55 and 58 with the claims under examination.

IV. Priority:

Although acknowledging receipt of a certified translation of the foreign priority document of this application, the Action alleges that because claims 40-54 and 59 have necessitated rejections under 35 U.S.C. § 112, first paragraph, the effective filing date of these claims is the filing date of this application, *i.e.,* October 26, 2006 (*see,* Office Action, pages 2-3).

Applicants have responded to the 35 U.S.C. § 112, first paragraph rejections below. Applicants submit that this application is entitled to its earliest priority date (*i.e.,* December 12,

2003), as well as the December 10, 2004 priority date of the International application of which the present application is a National Phase.

V. Rejection Under 35 U.S.C. § 102(b):

Claims 40-54 and 59 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fukishima *et al.* (U.S. Pat. Publ. No. 2004/058393) (*see,* Office Action, pages 3-6, section 9).

Amended independent claim 40 is drawn to a method for selecting a scFv multimer with thrombopoietin (TPO)-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating myeloproliferative leukemia virus oncogene (mpl) receptor. The method includes the steps of: identifying an antibody that binds to mpl receptor; providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence; producing a covalently linked scFv multimer comprising two copies of said light chain variable region sequence and two copies of said heavy chain variable region sequence, linked via linkers; testing the covalently linked scFv multimer for said TPO-like agonistic activity; and selecting the covalently linked scFv multimer if it binds to mpl receptor and exhibits said TPO-like agonistic activity at a level that is (i) greater than the level at which the antibody exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of said light chain variable region sequence linked via a linker to one copy of said heavy chain variable region sequence.

Amended independent claim 41 is drawn to a method for selecting a single-chain antibody with TPO-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating mpl receptor. The method includes: identifying an antibody that binds to mpl receptor; providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence; producing a single-chain polypeptide comprising two or more copies of the light chain variable region sequence and two or more copies of the heavy chain variable region sequence, linked via linkers; testing the single-chain polypeptide for said TPO-like agonistic activity; and selecting the single-chain polypeptide if it binds to mpl receptor and exhibits said TPO-like agonistic activity at a level that is (i) greater

than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the light chain variable region sequence linked via a linker to one copy of the heavy chain variable region sequence.

Amended independent claim 59 is directed to a method for selecting a single-chain polypeptide with enhanced TPO-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating mpl receptor. The method involves: identifying an antibody that binds to mpl receptor; providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence; producing a single-chain polypeptide comprising two or more copies of a humanized version of said light chain variable region sequence and two or more copies of a humanized version of said heavy chain variable region sequence, linked via linkers; testing the single-chain polypeptide for said TPO-like agonistic activity; and selecting the single-chain polypeptide if it binds to mpl receptor and exhibits said TPO-like agonistic activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of the humanized version of said light chain variable region sequence linked via a linker to one copy of the humanized version of said heavy chain variable region sequence.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Fukishima focuses primarily on Integrin associated protein (IAP) antibodies and teaches that certain IAP diabodies have greater apoptosis-inducing activity than the corresponding sc(Fv)$_2$s (*see,* [0262] and Fig. 43). Although Fukishima provides one example (Example 7) directed to anti-mpl receptor antibodies, this example is directed to scFvs and diabodies (*see,* [0304]-[0306]), and not the types of antibody structures produced by the claimed methods. This example teaches that anti-mpl receptor diabodies have greater TPO-like agonist activity than the corresponding scFv. There is no disclosure in Fukishima of any sc(Fv)$_2$ or covalently linked

scFv multimers that bind mpl receptor, let alone a comparison of the activity of such antibody species to the activity of corresponding diabodies, as required by the present claims. At the second Examiner's Interview conducted on November 18, 2009, the Examiners agreed that Fukishima does not anticipate the claims as presently amended. Applicants request that this rejection be withdrawn.

VI. Rejection Under 35 U.S.C. § 112, Second Paragraph:

Claims 40-54 and 59 are rejected under 35 U.S.C. § 112, second paragraph, as purportedly being indefinite (*see,* Office Action, pages 6-7, section 11).

(a) The Action states that the claim language regarding the nature of the diabody used as a comparator in claims 40, 41, and 59 is indefinite "because the claims do not identify the origination of the 'light chain variable region sequence' and the 'heavy chain variable region sequence' in the diabody." The Action asks: "Are these sequences the same sequences used to produce the multimer or single chain polypeptide or can they be sequences from another antibody?"

In response, Applicants note that independent claims 40, 41, and 59 have been amended to make clear that the comparator diabody comprises the same light chain variable region and heavy chain variable region sequences used to produce the scFv multimer or single chain polypeptide. In view of the present claim amendments, Applicants submit that claims 40, 41, and 59 fully comply with 35 U.S.C. § 112, second paragraph, and therefore request that this rejection be reconsidered and withdrawn.

(b) The Action alleges that the recitation "thrombopoietin-like agonist activity" in claims 44 and 46 is indefinite "because it is unclear and cannot be ascertained whether the activity being referred to agonizes thrombopoietin, whether the activity agonizes a molecular pathway in a similar manner to thrombopoietin, or if the agonist activity is thrombopoietin-like in some other way?"

Claims 44 and 46 have been canceled, so this rejection is moot as to those claims. As the phrase "thrombopoietin-like agonist activity" now appears in amended claims 40, 41 and 59, Applicants address this rejection as it may apply to those claims.

Claims 40, 41, and 59 recite, in relevant part, "TPO-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating mpl receptor." In view of the further detail provided regarding the nature of the TPO-like agonistic activity, Applicants respectfully contend that the rejection should not be applied to these claims.

VII. Rejection Under 35 U.S.C. § 112, New Matter:

Claims 40-54 and 59 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly adding new matter (*see,* Office Action, pages 7-10, section 13). The Action alleges that there is an apparent difference between the breadth of the claims and that of the disclosure for two reasons. First, the Action states that "the specification does not appear to provide any general disclosure that the methods as claimed would produce a subgenus of multimers or single chain polypeptides which exhibit 'activities' as instantly recited." Second, the Action states with respect to claim 40, that "while the specification discloses making the antibody into a 'single chain polypeptide', support for the broader recitation of a 'covalently linked scFv multimer', which could include e.g., cross-linked diabodies that were not disclosed in the specification, could not be found in the specification as filed."

Regarding the first point, Applicants note that the independent claims have been amended to recite a particular activity for the claimed scFv multimer and single-chain polypeptides: "TPO-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating mpl receptor." In view of the present amendment, taken together with the disclosure, *e.g.,* in Example 2.7 and at page 14, lines 29-35, Applicants submit that the application provides sufficient support for the pending claims.

Regarding the limitation "covalently linked scFv multimer" in claim 40(c), Applicants point the Examiner to the disclosure of non-peptide linkers at page 6, lines 30-32, and page 7, lines 17-24. It is also noted that claim 40 has been amended to limit the number of copies of the light and heavy chain variable region sequences to two each, as supported at page 2, lines 24-28.

In view of the foregoing, Applicants respectfully submit that no new matter has been added in the claims as presently amended, and therefore request reconsideration and withdrawal of this rejection.

VIII. Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description:

Claims 40-54 and 59 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement (*see,* Office Action, pages 10-14, section 14). In supporting this rejection, the Action makes two points: *first*, the claim language does not appear to find support in the specification as filed; and *second*, the claims broadly recite a genus of "antibody activities" and antibodies can have a diverse number of different and unpredictable activities depending on the epitope bound and immunoglobulin subclass (*see,* Office Action, pages 10-14, section 14). The first point was addressed in section VII above. Regarding the second point, Applicants note that the present amendments to claims 40, 41, and 59 specify a particular activity that is unquestionably supported by the application as filed. This was acknowledged by the Examiners in both Interviews.

Applicants submit that the amended claims fully comply with the written description requirement. Accordingly, it is respectfully requested that this rejection be reconsidered and withdrawn.

IX. Rejection Under 35 U.S.C. § 112, Enablement:

Claims 40-54 and 59 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement (*see,* Office Action, pages 14-17, section 15). The Action states that "[f]or the reasons set forth in the above rejection of the claims, as failing to satisfy the written description requirement, it has been submitted that the specification would amount to no more than an invitation to the skilled artisan to discover the identity of other processes encompassed by the claims." As Applicants understand it, the Examiners agreed during the Interviews that amending the claims as in the present amendment would be sufficient to overcome this ground of rejection. Applicants respectfully request that this rejection be reconsidered and withdrawn.

X. Information Disclosure Statement:

Applicants respectfully request that the Examiner consider the references listed on the PTO Form-1449 being submitted with this Amendment and initial and return this Form with the next Office Communication.

CONCLUSION

Applicants respectfully request withdrawal of all the rejections and allowance of the claims.

Other than the RCE filing fee and the fees for the two-month extension of time, no additional fees are believed to due with this filing. If Applicants are mistaken, please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0164US1.

Respectfully submitted,

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